ANNALSATS Articles in Press. Published on 03-June-2016 as 10.1513/AnnalsATS.201605-331PS

Towards an Earlier Diagnosis of Primary Ciliary Dyskinesia: Which Patients Should Undergo Detailed Diagnostic Testing?

Claudia E. Kuehni (1) and Jane S. Lucas (2, 3)

1) Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.

2) Primary Ciliary Dyskinesia Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3) NIHR Southampton Respiratory Biomedical Research Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.

Corresponding Author:
Jane Lucas
University of Southampton Faculty of Medicine - NIHR Southampton Respiratory Biomedical Research Unit
University of Southampton and University Hospital Southampton NHS Foundation Trust
Southampton SO16 6YD
United Kingdom of Great Britain and Northern Ireland
jlucas1@soton.ac.uk. +44(0)23 8120 6160

Disclosures: CEK and JSL are participants in the European Union's Seventh Framework Programme under EG-GA No.35404 BESTCILIA: Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia. They are Chair and Deputy Chair of COST Action BEAT-PCD: Better Evidence to Advance Therapeutic options for PCD (BM 1407) and are members of the ERS PCD Taskforce for PCD Diagnostics (ERS TF-2014-04). The views expressed in this manuscript do not reflect official views of these collaborations.

Key Words: primary ciliary dyskinesia, diagnosis, clinical features, epidemiology

Running Head: Identifying whom to refer for PCD diagnostic tests

Word Count: 2384

Abstract

Primary ciliary dyskinesia is a rare heterogeneous recessive genetic disorder of motile cilia, leading to chronic upper and lower respiratory symptoms. Prevalence is estimated at around 1:10,000, but many patients remain undiagnosed, while others receive the label incorrectly. Proper diagnosis is complicated by the fact that the key symptoms such as wet cough, chronic rhinitis and recurrent upper and lower respiratory infection, are common and nonspecific. There is no single gold standard test to diagnose PCD. Presently, the diagnosis is made in patients with a compatible medical history following a demanding combination of tests including nasal nitric oxide, high-speed video microscopy, transmission electron microscopy, genetics, and ciliary culture. These tests are costly and need sophisticated equipment and experienced staff, restricting use to highly specialised centers. Therefore, it would be desirable to have a screening test for identifying those patients who should undergo detailed diagnostic testing. Three recent studies focused on potential screening tools: one paper assessed the validity of nasal nitric oxide for screening, and two studies developed new symptom-based screening tools. These simple tools are welcome, and hopefully remind physicians whom to refer for definitive testing. However, they have been developed in tertiary care settings, where 10 to 50% of tested patients have PCD. Sensitivity and specificity of the tools are reasonable, but positive and negative predictive values may be poor in primary or secondary care settings. While these studies take an important step forward towards an earlier diagnosis of PCD, more remains to be done before we have tools tailored to different health care settings.

Abstract Word Count: 257

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Primary ciliary dyskinesia (PCD) is an inherited disease characterized by abnormal ciliary function and, in about 80% of cases, abnormal ciliary ultrastructure (1, 2). It affects mucociliary clearance and leads to a wide variety of symptoms primarily affecting the respiratory system, which usually present soon after birth (3). The key symptoms- -productive cough, chronic rhinitis and recurrent upper and lower respiratory tract infections--are all nonspecific and occur in many respiratory diseases, including common ones like asthma and COPD, and rare ones like cystic fibrosis and immune deficiency syndromes (4). Because embryonic nodal cilia determine left-right asymmetry, approximately half of PCD patients have situs inversus, and some have heterotaxic syndromes with or without cardiac malformations (5). Male infertility is common because sperm flagellae have a similar ultrastructure as cilia. Female infertility, renal malformations, hydrocephalus and retinitis pigmentosa are seen occasionally, but their incidence is unknown.

PCD is a rare disease. Its prevalence is difficult to determine because of limited representative data. Prevalence estimates for the general population vary between 1 in 2,000 to 1 in 40,000. Prevalence estimates of 1 in 2,000 are derived from certain populations with high proportions of consanguineous marriages (6).

Diagnosis of PCD is challenging. There is no single ‘gold standard’ diagnostic test. European Consensus guidelines (2009) recommend a combination of tests for symptomatic patients including measurement of nasal nitric oxide (nNO), high-speed video microscopy analysis (HSVMA) of ciliary beat frequency and pattern, and quantitative transmission electron microscopy (TEM) of ciliary ultrastructure(8). The European guidelines also suggest use of

additional tests such as immunofluorescence labelling of cilia proteins, pulmonary radioaerosol mucociliary clearance and genotyping.

Recent North American Consensus guidelines (2016) are not dissimilar, but place more emphasis on genetic tests and less reliance on functional studies using HSVMA (9). None of the available tests detects all patients with PCD. For instance, about 16%-20% of PCD patients have TEM without a detectable defect and some patients have a normal nNO (10, 11). HSVMA is more sensitive, but not sufficiently standardised to rule out PCD as a stand-alone test (12). Reanalysis following submerged or air-liquid interface (ALI) culture helps to exclude secondary ciliary dyskinesia (13). More than 30 PCD-causing genes have been discovered, which together explain about 70% of PCD cases (14).

In situations without a 'gold standard' diagnostic test, clinicians and researchers must determine diagnosis based on multiple test results (15, 16). The 3 diagnostic reference centers for PCD in England, work in close collaboration to diagnose PCD based on nNO, HSVMA and TEM (17, 18). Inconclusive and positive samples are reanalysed following culture. In North America, HSVM is not widely used, and PCD is diagnosed based on results from TEM, nNO and genetic testing (9, 16). All diagnostic tests for PCD are technically demanding, need up-to date equipment and well-trained staff with a high level of expertise. To allow technicians to acquire sufficient expertise with this rare disease, diagnostic facilities should be responsible for patient populations. For instance, in a region with a population of 1 million and an estimated prevalence of 1 in 10,000; we expect 100 persons to have PCD. Given the average life expectancy of 80 years, every year about 1 person will be newly diagnosed, if 100% of cases are diagnosed. In a region or country covering 10 million inhabitants, we expect a maximum of 10-

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12 new cases every year – this might be a minimal number to allow the diagnostic team to be familiar with positive TEM and HSVM findings, including difficult subtle cases.

PCD is Underdiagnosed

Although the estimated prevalence of PCD is around 1 in10,000 live births (19), a survey of paediatric pulmonologists from 26 European countries found that doctor-diagnosed cases were considerably less frequent in most countries and that half of the children were not diagnosed until school age. Diagnosis was particularly late in those with normal situs. Diagnostic testing and management of PCD was found to vary widely within Europe (20).

In the U.S., fewer than 1000 patients had an established diagnosis of PCD in 2013, which would correspond to an incidence of approximately 1in 315,000. The median age at diagnosis was 5 years (21). A study from Australia reported a median age at diagnosis of 6.4 years, and disturbingly found bronchiectasis already present in one third (22).

These studies did not take into consideration the larger adult population with 'missed' PCD. Delayed and overlooked diagnoses in North America, Europe and Australia shows that pediatricians are not thinking of this rare disease when encountering symptomatic patients. These findings are concerning because early detection and appropriate management might slow the progression of bronchiectasis, improve hearing to prevent speech and educational delays, and provide genetic counselling for families. The problem extends to adult practice. Anecdotal evidence suggests that many adult patients are managed in non-CF bronchiectasis

clinics, where cystic fibrosis and immunological causes are excluded by appropriate diagnostic studies, but testing for PCD is often not considered.

The Diagnostic Challenge

What can we do to improve the situation, so that patients with PCD are diagnosed at a young age and receiving appropriate treatment? Given the low prevalence of the disease, and the high costs for testing, it is impossible to perform the whole set of diagnostic tests in the whole population or even in all patients with compatible symptoms. It would even be very costly to test 6 to 12 percent of the population for PCD, the proportion of children and young adults with chronic wet cough (23, 24). Pulmonologists, neonatologists, otorhinolaryngologists, and pediatricians need guidance to identify patients whose complaints warrant extensive testing. Until now "clinical experience" was used to decide, which patients to refer for testing. The large proportion of undiagnosed PCD patients, and the reports from patients who were diagnosed after long delays, (7) shows that this strategy has not been very successful. A good screening test that filters out – among people with chronic respiratory symptoms – those most likely to have PCD, would be welcome.

Three recent publications have focused on this topic, including one published in this issue of *AnnalsATS* (25) (Table 1). Collins et al investigated the validity of nNO as screening test for PCD in hypothetical populations with different prevalence of PCD (26). Reports by Behan and colleagues (27) and Leigh and coauthors (25) both propose screening tools based on symptom scores

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Who Should be Referred for Diagnostic Testing?

In a short paper, Collins and coworkers investigated the validity of nNO in the population of 282 patients referred to one of the national PCD diagnostic centers in England. (26) Using a combination of tests, 11% of the referrals were finally diagnosed with PCD. Collins calculated sensitivity, specificity, positive and negative predictive values of nNO in this population, but also in hypothetical populations with a lower prevalence of PCD. He found that nNO performed well in his highly selected patients. However, in populations with a lower prevalence of PCD, the number of false positive cases identified by nNO would far out-weigh the true positives (26). If nNO was applied as a screening tool to the general population, it would lead to a huge number of patients wrongly referred to the expensive diagnostic services.

Leigh and coauthors studied a cohort of patients aged 18 years of age or younger referred to one of 7 specialized medical centers participating in the North American Genetic Disorders of Mucociliary Clearance Consortium because of a high suspicion of PCD (25). They investigated the performance of 5 individual, pre-defined clinical characteristics and various combinations these characteristics as predictors of PCD. They achieved this by comparing patients in whom PCD was confirmed by a hallmark ultrastructural defect or two mutations in a PCD-associated gene ('definite PCD', n=205) with patients, in whom PCD was excluded ('other disease/undefined, n=187), or in whom PCD remained probable but could not be confirmed ('probable PCD', n=142).

Among the 5 expert-defined symptoms, 4 were significantly more common in patients with definite PCD compared to 'other/undefined' patients. These were: neonatal respiratory

distress; chronic cough; chronic nasal congestion; and *situs inversus.* Recurrent otitis did not discriminate. Rewording the symptoms to make them more specific (for instance 'unexplained neonatal respiratory distress' instead of 'neonatal respiratory distress') decreased prevalence of the feature in both groups, and thus decreased sensitivity but increased specificity of the symptoms compared to the more general wording. The authors calculated sensitivity and specificity for each symptom alone, and for combinations of two, 3, and 4 symptoms. The combination of laterality defects and neonatal distress performed best, with a sensitivity of 34% and a specificity of 95%.

Recently, Behan and coworkers proposed another symptom score as a predictive tool for PCD (27). They included 641 patients referred for diagnostic evaluation to the PCD Diagnostic Centre in University Hospital Southampton (UHS), of whom 75 (12%) were confirmed to have PCD. The methodology differed from that employed by Leigh and colleagues. Rather than testing predefined predictors based on expert opinion, Behan and colleagues used a statistical approach to decide which of 27 questions recorded routinely during the PCD diagnostic clinic best predicted a diagnosis of PCD. Seven variables remained significantly associated with PCD in a multivariable logistic regression. As in the study by Leigh and colleagues, these included: *situs inversus*, neonatal chest symptoms, admission to the neonatal unit and rhinitis.

In contrast to Leigh's study, chronic cough was not a predictor of PCD, being common in those with and without the diagnosis. However, gestational age, congenital heart defects, and ear and hearing problems were predictive. The authors simplified the regression model into a

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short clinical tool, which they call PICADAR (the PrImary CiliARy DyskinesiA Rule (27)). They then performed an external validation study on an independent cohort.

The PICADAR score predicted with reasonable accuracy those who subsequently had a positive or negative test for PCD. For example, using a cut-off score of 6, PICADAR had 89% sensitivity and 83% specificity to differentiate PCD positive and negative patients in the derivation group, and 81% sensitivity and 76% specificity in the validation group. If patients with a score of <6 had not proceeded to further testing, 247 (82.6%) and 59 (75.6%) negative patients would have avoided formal testing at the diagnostic centers however, it is important to caution that 8 (11.4%) positive patients in the derivation group and 15 (18.8%) in the validation group would have been missed.

Extrapolation to Other Settings

Can the results from these two studies be extrapolated to other settings, for instance other countries, other specialty practices, such as otorhinolaryngology clinics, or other levels of care (e.g. primary care)? Only with great caution.

All 3 screening tests perform reasonably well in the setting of highly specialised referral practices, where the studies had been conducted (Table 1). The PICADAR study came from a national diagnostic center for PCD in England; with most patients being referred via secondary or specialist respiratory care and 12% were finally diagnosed with PCD. The setting for the North American study was even more selective. Their study comprised a diagnostic re-evaluation of a cohort of patients with a firm suspicion of PCD. Of 392 patients included in their

analysis, PCD was confirmed in 205 (52%), based on hallmark findings in transmission electron micrographs or the presence of two disease-causing mutations.

The validity of the predictive symptom score in these studies is influenced by several factors: First, the mix of patients determined by local referral habits: this determines which predictors will discriminate between patients. Second, the definition of PCD (i.e. the diagnostic gold standard): this affects the sensitivity of the score. Third, the prevalence of PCD within the patient population: this influences positive and negative predictive value of test results.

The first factor is illustrated nicely by the observation that chronic cough, a hallmark symptom of PCD, emerged as a significant predictor in the North American study but not in the UK study. This seeming paradox is explained by the fact, that chronic cough was a relative prerequisite for referral to the UK center and virtually every patient had it; thus cough did not discriminate between patients who finally were or were not diagnosed with PCD. The PICADAR score therefore should only be applied to patients with chronic cough. In analogy, we would expect that in a study conducted in an otorhinolaryngology department, chronic rhinitis would not have emerged as a useful predictor.

Secondly, as we lack a gold standard diagnostic test, both centers used a composite test for the final diagnosis. In PICADAR, this composite test included nNO, transmission electron microscopy, and HSVMA. In the US study, the diagnosis of PCD was based on hallmark findings on transmission electron microscopy or the presence of two disease-specific mutations. As PCD genes currently explain only 70% of PCD cases, and a significant proportion of patients have normal ciliary ultrastructure on transmission electron microscopy, this approach misses patients who therefore landed in the “probable/possible” category. Adding these cases in a

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sensitivity analysis did reduce sensitivity of the prognostic score, as illustrated in online table 1 in (25).

Thirdly, while sensitivity and specificity are independent of the prevalence of the disease, the positive and negative predictive values are strongly influenced by the prevalence of PCD among those referred for testing. For example, the combination of laterality defects and a history of neonatal distress had, in the US cohort (PCD prevalence of 52%), a sensitivity of 34% and a specificity of 95%. This translates into a positive predictive value of 88% and a negative predicted value of 57% (Table 1, Scenario 1).

In a cohort where only 12% of the referral group has PCD, as in the UK study, the positive and negative predictive values change to 48% and 91% respectively (Table 1, Scenario 2). If only 1 in 100 patients have PCD, as might be the case in respiratory patients seen in secondary care (Table 1, Scenario 3), or 1 in 10,000, as in the general population (Table 1, Scenario 4), the positive predictive value would fall to 6% and 0.07% respectively. The same can be observed for the PICADAR tool and nNO: the positive predictive value, e.g. the likelihood that a positively screened patient has PCD, falls with decreasing prevalence of PCD in the study population.

As is the case with cystic fibrosis, there are mild or atypical phenotypes of inherited ciliary dysfunction, many of which have not yet been fully characterized. Some may manifest later in childhood or first in adults. A limitation of studies investigating diagnostic and screening tests for PCD is that they systematically exclude patients with atypical symptoms because the diagnosis has not been considered. For example, patients with defects effecting the central apparatus of the cilia will not have situs abnormalities and are thereby systematically less likely

to score highly on either of the symptom screening tools. Similarly there are a small number of patients whose PCD is caused by mutations associated with normal nasal nitric oxide levels. Adults might often not know about neonatal symptoms, or at least not report them proactively, which again decreases their scores in both instruments. Furthermore, 'atypical' patients might be falsely labelled as 'PCD negative' by detailed diagnostic testing because current diagnostic tests (e.g. TEM and genetics) fail to identify them correctly.

Conclusions

In summary, two recent studies have developed symptom-based tools that can be used to identify patients at high risk for primary ciliary dyskinesia. Both are welcomed as they will raise awareness of the symptoms of PCD amongst non-specialists. Before they are put into widespread use, the tools require validation in different clinical settings, for instance, primary, secondary and tertiary care, in pediatric pulmonology, adult pulmonology, or otorhinolaryngology. We can then refine and adapt the prediction tools for these settings.

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Acknowledgements

We thank Florian Halbeisen and Myrona Goutaki, University of Bern, for help with calculations and comments on previous versions of this manuscript.

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ANNALSATS Articles in Press. Published on 03-June-2016 as 10.1513/AnnalsATS.201605-331PS

Table 1: Relationship between PPV and NPV and the pretest probability of PCD (proportion of patients with PCD in the tested population), for three proposed screening tests for PCD: nasal NO, PICADAR (cut-off >6), and clinical symptom score (combination of neonatal distress and laterality defects.

Publication	Screening instrument			Scenario 1 US referral group PCD prevalence = 52%		Scenario 2 UK referral group PCD prevalence = 12%		Scenario 3 Secondary care PCD prevalence = 1%		Scenario 4 General population PCD prevalence=0.01%	
		Sensitivity	Specificity	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Collins et al (26)	nNO (cut-off 77nl/min)	94%	84%	86%	92%	44%	99%	6%	99.9%	0.06%	99.9%
Behan et al (27)	PICADAR tool (cut-off score >6)	76%	94%	93%	78%	63%	97%	11%	99.7%	0.1%	99.9%
Leigh et al (25)	Symptoms score (neonatal distress & laterality defects)	34%	95%	88%	57%	48%	91%	6%	99.3%	0.07%	99.9%

Legend: PPV: positive predictive value; NPV negative predictive value. Sensitivity and specificity do not vary with disease prevalence. Columns represent four different scenarios: 1) 52% of patients have PCD, as in (25); 2) 12% of patients have PCD as in (27); 3) 1% of patients has PCD as in patients with chronic respiratory symptoms presenting to secondary care; 4) 0.01% of patients have PCD as in the general population.